REMARKS

This is intended as a full and complete response to the Final Office Action dated July 29, 2008, having a shortened statutory period for response set to expire on October 29, 2008. Please reconsider the claims pending in the application for reasons discussed below.

Claim Rejections - 35 U.S.C. § 103

Claims 1-3, 5-11, 17-20, 22-24, 27, and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over *Parikh et al.* (US 2002/0106403; "Parikh") in view of *Caruso et al.* (EP 1 116 516; "Caruso").

Claims 1, 18 and 24 recite a dosage and methods in which a shell has "high permeability for the slightly soluble active ingredient." However, Applicants submit that the Examiner erroneously alleges that Parikh discloses fast releasing microcapsules comprising a core and a shell and that the shell has a high permeability. Since Parikh as set forth herein does not teach such a shell, the proposed modification to the composition of the shell is also erroneous and cannot establish obviousness.

Parikh describes a solid dosage form with primary particles **stabilized** with one or more surface **modifiers** (paragraph [0013]). The surface modifier can be for example a phospholipid (paragraph [0014]). The surface modifier does not, however, form a shell. Rather, the surface modifier is merely associated with the outer surface of the primary particles for shielding the hydrophobic outer surface of the primary particles. The shielding stabilizes the hydrophobic primary particles in an aqueous solution so that an aqueous suspension can be formed. The suspension is later mixed with matrix-forming bulking and/or releasing agents and then dried to form a dosage form (paragraph [0018]).

Once the primary particles are released from the matrix of the dosage form, the water-insoluble compound forming the primary particles dissolves. The surface modifier is released from the primary particles when the outer layer of the primary particle dissolves. Due to their amphiphilic nature, the surface modifier is associated with the

outer surface of the primary particle through its hydrophobic part. When dissolution starts, the surface modifier is released together with the molecules of the water-insoluble compound to which it is associated. Hence, the surface modifier disappears during the initial stage of dissolution. This means that the compound does not diffuse through the surface modifier but is released together with the surface modifier. In fact, the surface modifier improves dissolution of the water-insoluble compound by forming a water-soluble complex with molecules of the compound. Therefore, dissolution of the water-insoluble compound takes place by common disintegration of the water-insoluble compound and the surface modifier. Once the surface modifier is desorbed, an aggregation of the primary particles occurs.

Therefore, the surface modifier merely associates with, and **adsorbs** to, the surface of the primary particles as stated in the last sentence of paragraph [0010], without forming a self-supporting stable shell capable of providing any permeability attributes.

Since the adsorbed surface modifier dissolves during dissolution of the primary particle, it does not provide a diffusion barrier and does not control the release of the compound from the primary particle. Paragraph [0025] of Parikh particularly refers to this point by stating:

> The rate of *dissolution* or release of the active ingredient may also be affected by the nature of the medicament and the *microparticle composition* such that it may be rapid (5-60 sec) or intermediate (on the order of 75% disintegration in 15 minutes) or sustained-released. (Emphasis added)

Hence, Parikh does not disclose that the compound diffuses through a shell but merely dissolves. Furthermore, the particle composition and not the surface modifier controls the release rate.

In fact, the surface modifier forms a diffusion barrier for the water-insoluble compound. From a thermodynamic point of view, it is energetically unfavorable for the compound to diffuse through the layer of adsorbed surface modifier into an aqueous environment. The hydrophobic water-insoluble compound is shielded from the aqueous environment by the surface modifier which is energetically favored. Hence, no diffusion

through the layer of surface modifier occurs and the surface modifier acts as diffusion barrier. This also becomes evident from the point that the surface modifier **stabilizes** the primary particle in the suspension prior to forming the dosage. If the surface modifier allowed diffusion, the primary particles would dissolve in the suspension and no dosage with primary particles could be formed. This clearly shows that **no** diffusion occurs through the layer of adsorbed surface modifier in an aqueous environment.

To summarize, Parikh describes use of amphiphilic surface modifiers to stabilize primary particles in an aqueous solution. The amphiphilic surface modifiers form a diffusion barrier for the water-insoluble compound forming the primary particles. No shell having a high permeability for the compound is formed by the surface modifiers. The primary particles dissolve by desorption of the surface modifiers.

Different to Parikh, present claim 1 calls for *"capsules"* comprising a core and a shell. The shell formed by a complex of at least one polyelectrolyte and a counter ion is stable and highly permeable as stated on page 9, lines 20-25 of the current application. The shell defined in claim 1 is therefore stable and allows diffusion and release of the active ingredient. The shell remains stable and therefore maintains a stable aqueous suspension **during** release of the active agent. Different thereto, Parikh's particles tend to aggregate after initial release since the associated surface modifier is released together with water-insoluble molecules from the outer surface so that the primary particles loose their surface modification.

With respect to combining the teachings of Parikh and Caruso as proposed by the Examiner, Applicants submit that any such combination is erroneous since Caruso uses a completely different approach than Parikh.

Parikh adsorbs amphiphilic surface modifiers to stabilize primary particles. The amphiphilic surface modifiers also improve disintegration of the primary particles by formation of water-soluble complexes between the surface modifiers and molecules of the water-insoluble compound. Parikh states in paragraph [0025] that a rapid **dissolution** may occur which is only possible when such complexes are formed. Since the solubility of the water-insoluble compound is small, dissolution without amphiphilic surface modifiers would take a very long time despite the fact that aggregation would occur, which further hinders dissolution. Parikh does not disclose a shell but merely

adsorbed surface modifiers. Furthermore, Parikh relates the release time with the particle composition.

Different therefore, a polyelectrolyte cover is used by Caruso for obtaining a **constant release rate over a long time period**, as stated in paragraph [0012] on page 3, lines 19-20. Therefore, only a sustained release is described by Caruso; see for example page 3, lines 29-30:

> The process of the invention is particularly suitable to prepare release systems, which release *a small amount* of active substance constantly of an *extended* period of time. Such a system advantageously comprises a *high diffusion barrier* across the wall of the capsule, which results in a small amount of released substance with respect to the amount of substance which can be supplemented in the same period of time by solubilization of solid material within the capsule. Such release systems are particularly useful in hormone therapy wherein the constant release of small amounts of active substance is required. (Emphasis added)

Paragraph [0032] on page 5 of the Caruso reference also refers to a **controlled** release of the encapsulated material. Hence, Caruso describes providing a **high** diffusion barrier for obtaining a sustained release of the encapsulated material. A skilled person would be therefore, when considering Caruso, directed to sustained release systems only.

Different thereto, claim 1 recites a shell having a material with high permeability for the slightly soluble active ingredient.

The Examiner particularly refers to paragraphs [0032] and [0053] of the Caruso reference and alleges that Caruso discloses controlling the permeability and porosity of the capsules. Paragraph [0032] merely states that the porosity can be controlled but fails to describe to what extent. Furthermore, paragraph [0053] describes a method for dissolving the microcrystal templates for forming hollow capsules and not the release kinetics of active ingredients in a physiological environment. Moreover, the release experiments described in paragraph [0053] include a water/ethanol mixture. A water

ethanol mixture is by no means a physiological environment. The release experiments described in paragraph [0053] are therefore not comparable with the release experiments described in the present application. A skilled person, when considering the release of an active ingredient in a human body would never consider the release kinetics obtained in a water/ethanol mixture.

In connection with release time for forming hollow capsules, paragraph [0053] of Caruso states that "the release rate could be altered by varying the *ratio* of ethanol to water in the dissolving medium" (Emphasis added). Hence, according to paragraph [0053] the release rate is determined by the nature of the **external** solute. For pharmaceutical applications, the physiological environment cannot be changed so that it is irrelevant that the nature of the external solute determines the release rate.

Furthermore, Caruso attributes high release rates to the external solute while Parikh to the particle composition. Caruso states in paragraph [0053] that

> the rate of removal was largely unaffected by the type of surfactant used (positive or negative, C12-C14 chain length), nor was it influenced by the presence of 5-10 polyelectrolyte layers.

The polyelectrolyte layer and the surfactant, different to the general statement in Caruso, do not influence the release rate. Only the type of the **external** solute is relevant. Therefore, Caruso and Parikh are based on different models for the release rate. Since the actual experiments described by Caruso show that the polyelectrolyte layer **does not** influence the release rate, the statement of the Examiner that a skilled person would combine Parikh and Caruso "for the predictable results of controlling the release rate" is baseless.

Moreover, the release rate is significantly reduced when the amount of ethanol is reduced, as shown in paragraph [0053] of Caruso. For example, the release rate is about 100 times smaller when only a 5 vol% aqueous ethanol solution is used. Consequently, if no ethanol is used to have a physiologic environment, the release time would even be longer. These findings correspond to the general statement in Caruso, see paragraphs [0012] and [0038] discussed above, that the capsules are suitable for **sustained** release. In view of the foregoing, a skilled person would therefore not

combine Parikh and Caruso to form fast-releasing capsules having a **high** permeability for a slightly soluble active ingredient.

Therefore, Parikh and Caruso fail to render obvious claims 1, 18 or 24 or any claims dependent thereon. Accordingly, Applicants request withdrawal of the rejection and allowance of claims 1-3, 5-11, 17-20, 22-24, 27, and 29.

Claims 4, 25, and 28 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Parikh and Caruso in view of *Green et al.* (US 2001/0055611). Claims 12 and 21 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Parikh and Caruso in view of *Virgalitto et al.* (US 2005/0089548). *Green et al.* and *Virgalitto et al.* fail to overcome the deficiencies of Parikh and Caruso as discussed herein with respect to the independent claims from which claims 4, 12, 21, 25, and 28 depend. Accordingly, Applicants request withdrawal of the rejection and allowance of these claims.

Conclusion

Having addressed all issues set out in the office action, Applicants respectfully submit that the claims are in condition for allowance and respectfully request that the claims be allowed.

Respectfully submitted,

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